



UNITED STATES PATENT AND TRADEMARK OFFICE

cl
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,280	02/21/2002	Avi J. Ashkenazi	P1007R1C1	2465

9157 7590 04/11/2006
GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
----------	--------------

1644

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/081,280	Applicant(s) ASHKENAZI, AVI J.	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 January 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 46-65 is/are pending in the application.
- 4a) Of the above claim(s) 56-63 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 46-55 and 64-65 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/17/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 46-65 are pending.
2. Claims 56-63 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.
3. Claims 46-55 and 64-65, drawn to a method of blocking or inhibiting Apo-3 receptor using anti-Apo-3 antibody are being acted upon in this Office Action.
4. In view of the amendment filed 1/17/06, the following rejections remain.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 46-55 and 64-65 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO: 6; the death domain of Apo-3 consisting of the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody, **does not** reasonably provide enablement for (1) a method of blocking or inhibiting Apo-3 receptor comprising exposing human cells expressing Apo-3 receptor to an effective amount of any anti-Apo-3 antibody, any antibody such as chimeric antibody, humanized antibody, monovalent antibody, labeled anti-Apo-3 antibody, wherein said antibody comprises an antigen binding site which binds to Apo-3 receptor comprising SEQ ID NO: 6 or any "immunogenic fragment" of SEQ ID NO: 6, wherein upon binding the Apo-3 receptor polypeptide, the anti-Apo-3 antibody blocks or inhibits Apo-3 receptor induced apoptosis in *any* human cells or Apo-3 receptor activation of NF-kB in human cells, (2) a method of blocking or inhibiting Apo-3 receptor comprising exposing human cells

Art Unit: 1644

expressing Apo-3 receptor to an effective amount of any anti-Apo-3 antibody, any antibody such as chimeric antibody, humanized antibody, monovalent antibody, labeled anti-Apo-3 antibody, wherein said antibody comprises an antigen binding site which binds to Apo-3 receptor comprising SEQ ID NO:6 or any “immunogenic fragment” of SEQ ID NO: 6, wherein upon binding the Apo-3 receptor polypeptide, the anti-Apo-3 antibody blocks or inhibits Apo-3 receptor induced apoptosis in human cells or Apo-3 receptor activation of NF- κ B in human cells wherein said human cells are exposed to said anti-Apo-3 antibody in vivo as set forth in claims 46-55 and 64-66. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consists the amino acid residues 25 to 198 of SEQ ID NO: 6, the death domain of Apo-3 consists the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody. The specification further discloses the antibody *may be employed* to activate or stimulate apoptosis in cancer cells. Alternatively, antagonist antibodies *may be used* to block excessive apoptosis (for instance in neurodegenerative disease) or block potential autoimmune/inflammatory effects of Apo-3 resulting from NF- κ B activation (page 62, lines 1-8, in particular).

However, the specification does not teach how to make any “antagonist antibody” having the properties of blocking excessive apoptosis *in vivo* for treating any neurological disease or blocking any Apo-3 receptor mediated activation of NF- κ B activation in vivo for treating

autoimmune/inflammatory effects associated with NF- κ B activation in vivo. There is insufficient guidance as to the epitope to which the antibody binds such that the antibody blocks or inhibits apoptosis in any human cells in the claimed method. The immunogenic fragment of SEQ ID NO: 6 could be a region within the trans-membrane domain. It is not clear if antibody binding to such region could inhibit apoptosis or block activation of NF- κ B in any human cells. If the immunogenic fragment of SEQ ID NO: 6 is an intracellular domain of Apo-3 receptor, any antibody that binds specifically to the intracellular domain require crossing the cell membrane. It is not clear how antibody such as chimeric, humanized, and labeled antibody penetrates the cell membrane and binds to specifically to the intracellular region of the receptor, let alone the right cell type in vivo.

Further, the term "comprising" is open-end. It expands the amino acid residues 25 to 198 of SEQ ID NO: 6 or amino acid residues 338 to 417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added and whether the resulting antibody still binds specifically to Apo-3 receptor comprising SEQ ID NO: 6, let alone the antibody may be used to inhibit apoptosis or NF- κ B activation in vivo. Further, the specification is silent with respect to which particular neurodegenerative disease is associated with Apo-3 mediated apoptosis and which particular autoimmune disease is associated with Apo-3 mediated activation of NF- κ B activation.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Kuby et al teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment may result in antibody specificity that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza et al teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Even if the antibody binds to the extracellular domain of the Apo-3 receptor comprising SEQ ID NO: 6, there is no evidence that the claimed antibody blocks Apo-3 receptor mediated apoptosis.

Coney et al teach antibody such as anti-Apo-1 antibody that binds to Apo-1 or Fas, a member of the NGFR1 super family, induces apoptosis of cells expressing the APO-1 receptor, rather than inhibiting apoptosis (see abstract, in particular). Coney et al further teach that such antibody might only be therapeutically when the antibody can be targeted to cells expressing said receptor such as tumor cells.

Given the unlimited undisclosed antigen binding site to which the antibody binds, there is a lack of working example demonstrating that the anti Apo-3 that binds only to human Apo-3 comprising SEQ ID NO: 6 or any fragment thereof could inhibit apoptosis of any Apo-3 receptor expressed in any mammalian cells in vitro, let alone inhibit apoptosis in vivo for treatment of any neurological disease or treating any autoimmune/ inflammatory effects as a result of Apo-3 mediated NF- κ B activation.

With regard to claims 52-53, there is insufficient guidance as how an anti-Apo-3 antibody labeled with a "detectable moiety" such as radioisotope, fluorescent compound or chemiluminescent compound could be used to "blocks or inhibits apoptosis" or "blocks or inhibits" Apo-3 receptor activation of NF- κ B in mammalian cells.

With regard to claim 65, in addition to the problem of "comprising" mentioned above, the amino acid residues 338 to 417 of SEQ ID NO: 6 is a death domain of the Apo-3 receptor, which locates within the mammalian cell. However, antibody such as Apo-3 antibody is a large molecule that does not get inside the cell, especially cells in vivo. There is insufficient guidance as how the antibody such as Apo-3 antibody that binds to the death domain within the cell in vitro, much less the antibody binds to the death domain of any mammalian cell in vivo.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/17/06 have been fully considered but are not found persuasive.

Applicants' position is that the claimed antibodies are both structurally and functionally limited. They are structurally limited, for example, because an antigen binding site that binds to an Apo-3 receptor polypeptide comprising SEQ ID NO:6 or an immunogenic fragment thereof is required. They are functionally limited, for example, because blocking or inhibition of Apo-receptor induced apoptosis or Apo-3 receptor activation of NF-kB is required. The specification adequately teaches one of skill in the art how to make and use such antibodies. For example, the specification identifies and characterizes the Apo-3 receptor both structurally and functionally. See, e.g., SEQ ID NO:6 and Examples 5-10. In addition, methods are described in the specification for preparing polyclonal, monoclonal, humanized, bispecific and heteroconjugate antibodies. See, e.g., specification pages 53-61. Based on the teachings in the specification and the knowledge in the art at the time of filing, the subset of antibodies defined in the claims are contemplated and enabled by the present disclosure.

The fact that SEQ ID NO:6 defines a polypeptide having 417 amino acid residues (i.e., the claims contain open-ended "comprising" language) is not determinative of undue experimentation because making and using the antibodies within the scope of the claims involves both structural and functional limitations. As indicated, for example, on page 54, "the immunizing agent will typically include the Apo-3 polypeptide immunogen encompasses "the native sequence Apo-3 and Apo-3 variants," including Apo-3 fragments, See e.g., at pages 13-14. The claims specify that when the antibody binds an Apo-3 fragment, it must be an immunogenic Apo-3 fragment and the resulting antibody must block or inhibit, for example, apoptosis. Experimentation may not be considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding direction of experimentation. The Examiner has appeared to read a "treating" limitation into the present claims, e.g., "the specification does not teach how to make any 'antagonist antibody' ...for treating any neurological disease or ... for treating autoimmune/inflammatory effect.", see page 5 of Office Action. This is inappropriate as the claims require only "blocking or inhibiting" certain activities of the Apo-3 receptor. The fact that certain conditions may be treated utilizing the methods of the present invention is irrelevant to the issue of enablement because treatment is not a requirement of the claims. As such, the citation of Convey et al reference is unavailing. With regard to claims 52-53 the Examiner questions how a labeled antibody can effect the blocking or inhibition required in the present claims. See Office action, page 6. The applicant respectfully submits that this added limitation could be readily and routinely performed by one of skill in the art. It is well

known in the art that an antibody can be labeled without affecting its reactivity or binding specificity in, for example, a sandwich assay, a competitive binding assay or an immunoprecipitation assay. See, e.g., specification at page 62. This antibody may be labeled and used to bind a receptor, for example, an Apo-3 polypeptide receptor. Although complement may be affected due to the means utilized to label the antibody, complement is not required to fulfill, for example, the blocking limitation of the claims. With regard to claim 65, the Examiner questions how an antibody can bind the disclosed death domain since it lies within the intracellular domain of the Apo-3 polypeptide. Although the present disclosure discusses secreted active forms of Apo-3 that can be blocked or inhibited utilizing an anti-Apo-3 antibody, the requirement for secretion is not required in the claim. Moreover, an anti-Apo-3 intrabody, a type of antibody well-known in the art at the time of filing, could have been routinely utilized to target intracellular protein regions such as the death domain. In this regard, the Applicant notes that the term "antibody" is used in its broadest sense in the specification. Applicant, nevertheless, has amended claim 65, as shown above, to clarify the presence of the recited death domain in the Apo-3 polypeptide provided in claim 64. The cancellation of claim 66 renders the rejection of the claim moot.

In response, the claimed method encompasses a method of blocking or inhibiting Apo-3 receptor using any anti-Apo-3 antibody that binds to Apo-3 receptor comprising SEQ ID NO: 6 or any immunogenic fragment thereof in vitro and/or in vivo (claim 54) in human cells expressing Apo-3 receptor.

The term "antibody" as defined by the specification at page 17 is used in the broadest sense and specifically covers single monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies) and antibody compositions with polypeptidic specificity.

The term "Biologically active" and "desired biological activity" as defined in the specification at page 19 is to mean having the ability to modulate apoptosis (either in an agonistic manner by inducing or stimulating apoptosis, or in an antagonistic manner by reducing or inhibiting apoptosis) in at least one type of mammalian cell in vivo or ex vivo.

The intended use of the "agonistic Apo-3 antibodies, for instance, may be employed to activate or stimulate apoptosis in cancer cells. Alternatively, antagonistic antibodies may be used to block excessive apoptosis (for instance in neurodegenerative disease) or to block potential autoimmune inflammatory effects of Apo-3 resulting from NF-KB activation and/or JNK activation. The antibodies may further be used in diagnostic assays. Apo-3 antibodies also are

useful for the affinity purification of Apo-3 from recombinant cell culture or natural sources” (page 62 of specification).

However, the specification does not teach how to make any “antagonist antibody” having the properties of blocking excessive apoptosis in vivo for treating any neurological disease or blocking any Apo-3 receptor mediated activation of NF- κ B activation in vivo for treating autoimmune/inflammatory effects associated with NF- κ B activation in vivo. There is insufficient guidance as to the epitope to which the antibody binds such that the antibody blocks or inhibits apoptosis in any human cells in the claimed method. The immunogenic fragment of SEQ ID NO: 6 could be any region or a region within the trans-membrane domain. It is not clear if antibody binding to such region could inhibit apoptosis or block activation of NF- κ B in any human cells. If the immunogenic fragment of SEQ ID NO: 6 is an intracellular domain of Apo-3 receptor, any antibody that binds specifically to the intracellular domain require crossing the cell membrane. It is not clear how antibody such as chimeric, humanized, and labeled antibody penetrates the cell membrane and binds to specifically to the intracellular region of the receptor, let alone the right cell type in vivo. Further, how is the labeled Apo-3 receptor antibody having a detectable moiety such as radioisotope, fluorescent compound or chemiluminescent compound connects to a method of blocking or inhibiting Apo-3 receptor induced apoptosis or Apo-3 receptor activation of NF- κ B? Further, the term “comprising” is open-end. It expands the amino acid residues 338 to 417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added and whether the resulting antibody in the claimed method still binds specifically to Apo-3 receptor comprising SEQ ID NO: 6, let alone the antibody may be used to inhibit Apo-3 induced apoptosis or NF- κ B activation in vivo. In other words, the antibody may binds to the extra amino acids at either or both ends instead of residues 338 to 417 of SEQ ID NO: 6. Further, the specification is silent with respect to which particular neurodegenerative disease is associated with Apo-3 mediated apoptosis and which particular autoimmune disease is associated with Apo-3 mediated activation of NF- κ B activation.

Likewise, the specification does not teach how to make any “agonist antibody” having the properties of stimulating apoptosis in cancer cells in humans. There is not a single antibody in the specification as filed showing either agonist activity or antagonist activity. The specification does not teach how to make anti-Apo-3 intrabody, much less targeting the Apo-3 antibody to the appropriate cell type in vivo, in turn, would be useful for blocking or inhibiting Apo-3 receptor mediated apoptosis or NF κ B activation. It is not routine to stimulate apoptosis in

cancer cells in vivo using any undisclosed anti-Apo-3. It is also not routine to inhibit apoptosis in neurodegenerative disease such as Alzheimer's disease using any undisclosed anti-Apo-3 antibody. Given the unlimited number of anti-Apo-3 antibody, it is unpredictable which anti-Apo-3 antibody is useful for the claimed method to block or inhibit Apo-3 receptor activation in vivo in the absence of in vivo working example. As such, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

7. Claims 46-55 and 64-65 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of blocking or inhibiting Apo-3 receptor using any Apo-3 antibody comprising any antigen binding site which binds to any "immunogenic fragment" of Apo-3 polypeptide comprising SEQ ID NO: 6, any Apo-3 receptor "comprises" amino acid residues 25 to 198 of SEQ ID NO: 6 and any Apo-3 receptor "comprises" amino acid residues 338-417 of SEQ ID NO: 6, any soluble, truncated or secreted form of any Apo-3 receptor for the claimed method of blocking or inhibiting Apo-3 receptor induced apoptosis or Apo-3 receptor activation of NFκB activation in vitro or in vivo.

The specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO: 47, the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO: 6, and the death domain of Apo-3 consisting of the amino residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody. The specification further discloses the antibody *may be employed* to activate or stimulate apoptosis in cancer cells. Alternatively, antagonist antibodies *may be used* to block excessive apoptosis (for instance in neurodegenerative disease) or block potential autoimmune/inflammatory effects of Apo-3 resulting from NF-κB activation (page 62, lines 1-8, in particular).

With the exception of the specific antibody mentioned above for a method of affinity purification of Apo-3 from recombinant cell culture or natural sources or a method of detection

Art Unit: 1644

assay, there is insufficient written description about any and all Apo-3 antibody that has the property of blocking or inhibiting Apo-3 receptor induced apoptosis and/or Apo-3 receptor activation of NFκB activation for the claimed method. Further, the term "comprising" is open-ended. It expands the amino acid residues 25 to 198 of SEQ ID NO: 6 or amino acid residues 338 to 417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is inadequate written description about which amino acids to be added and whether the resulting antibody still binds specifically to Apo-3 receptor comprising SEQ ID NO: 6, in turn, may be useful for inhibiting apoptosis or NF-κB activation in mammalian cells in vitro or in vivo.

The specification discloses only antibody that binds only to human Apo-3 receptor, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of anti-Apo-3 antibody for the claimed method. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/17/06 have been fully considered but are not found persuasive.

Applicants' position is that it is important to note that the Examiner has indicated that "the specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized [sic] an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO:47, the applicant assumes that since SEQ ID NO: 47 does not appear in the present application, the Examiner intended to refer to SEQ ID NO: 6 instead of SEQ ID NO: 47, the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO:6, the death domain of Apo-3 consisting of the amino acid residues 338 to 417 of SEQ ID NO: 6 and a method of detecting Apo-3 using said antibody. Moreover, the Examiner acknowledges written description for the use of these antibodies to "block excessive apoptosis" or "block potential autoimmune inflammatory effects of Apo-3 resulting from NF-AB activation." See id. The present claims involve the use of an antibody to human Apo-3. It is undisputed that the present specification set forth the specific amino acid sequence (SEQ ID NO: 6) for human Apo-3, including the location

Art Unit: 1644

and boundaries of several domain in the polypeptide. Antibodies to Apo-3 polypeptides (see, e.g., Example 6, 7 and 8) and the claims include corresponding functional limitations.

In response, Applicant's assumption is correct that the Examiner refers to antibody that binds specifically to SEQ ID NO: 6 instead of SEQ ID NO: 47 for the claimed method. The examiner apology for the typographical error.

The instant claims encompasses a method of blocking or inhibiting Apo-3 receptor using any anti-Apo-3 antibody that binds to any immunogenic fragment of SEQ ID NO: 6 in vitro and in vivo (claim 54) in human cells expressing Apo-3 receptor.

The issue here is whether the specification has a written support for any and all antibody that binds specifically to any fragment of Apo-3 receptor, any Apo-3 receptor "comprises" amino acid residues 25 to 198 of SEQ ID NO: 6 or any Apo-3 receptor "comprises" amino acid residues 338-417 of SEQ ID NO: 6 or Apo-3 comprising SEQ ID NO: 6 having *antagonist* activity or agonistic activity for the claimed method. There is inadequate written description about the immunogenic fragment to which the antibody binds such that it resulted in inhibiting or blocking Apo-3 receptor induced apoptosis in human cells in vitro or in vivo. There is inadequate written description about the immunogenic fragment to which the antibody binds such that it resulted in inhibiting or blocking Apo-3 receptor activation of NF-kB in human cells in vitro or in vivo. Further, the term "comprises" is open-ended. It expands the amino acid residues 25 to 198 of SEQ ID NO: 6 or amino acid residues 338-417 of SEQ ID NO: 6 to include additional amino acids at either or both ends. There is inadequate written description about the amino acids to be added, much less the binding specificity of the antibody for the claimed method. Given the unlimited number of antibody to Apo-3, there is inadequate written description about the binding specificity associated with the structure, i.e., CDRs 1-3 of light chain and CDRs 1-3 of the heavy chain of any and all antibody having activity, such as inhibiting or blocking App-3 receptor induced apoptosis or inhibiting or blocking Apo-3 receptor activation of NF-kB for the claimed method. With regard to examples 6, 7 and 8, none of the examples demonstrates the use of antibody that binds to Apo-3 to block or inhibit Apo-3 receptor induced apoptosis or to block/inhibit Apo-3 receptor activation of NF-kB in human cells as required by instant claims as argued.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Art Unit: 1644

9. Claims 52-53 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The “antibody is labeled with a detectable moiety” in claim 53 and “the antibody is labeled with a detectable moiety such as radioisotope, fluorescent compound or chemiluminescent compound” in claim 54 are ambiguous and indefinite because it is not clear to one of ordinary skill in the art how a labeled Apo-3 antibody could block or inhibit Apo-3 receptor induced apoptosis in mammalian cells or how a labeled antibody blocks or inhibits Apo-3 receptor activation of NFκB in mammalian cells. The specification discloses labeled Apo-3 antibody is for detecting Apo-3 in mammalian cells, NOT to block apoptosis or activation of NFκB in mammalian cells. Further, the labeled antibody in claims 52 and 53 has no antecedent basis in the *method of blocking or inhibiting Apo-3 receptor* as recited in base claim 46. Base claim 46 does not recite a method of detecting Apo-3 receptor... using labeled anti-Apo-3 antibody.

Applicants’ arguments filed 1/17/06 have been fully considered but are not found persuasive.

Applicants’ position is that the Examiner is interpreting an antibody used to block or inhibit Apo-3 receptor induced apoptosis or Apo-3 receptor activation of NFκB as mutually exclusive of anti-Apo-3 antibodies useful to detect Apo-3 in mammalian cells. The specification and the claims do not require this interpretation and one of skill in the art would not interpret these categories as mutually exclusive. The overlap in the antibody categories renders them definite since one could readily determine what antibodies have the requisite blocking or inhibiting activities and therefore fall within the scope of the claims.

In response, the labeled antibody in claims 52 and 53 has no antecedent basis in the *method of blocking or inhibiting Apo-3 receptor* as recited in base claim 46. Base claim 46 does not recite a method of detecting Apo-3 receptor... using labeled anti-Apo-3 antibody.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1644

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

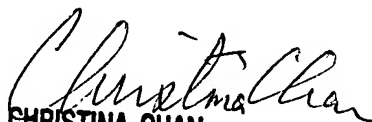
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

March 31, 2006


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600